Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' amendment of 26 January 2006 is acknowledged. Claim 44 is amended and the amendment made of record.

Claims 1-60 and 62-83 are pending in the instant application. Claims 1-43, 46-58 and 62-83 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 44, 45, 59 and 60 are under consideration, wherein the selector codon may be an amber, ochre or opal codon.

Withdrawn Rejections

The rejection of Claims 44, 45, 59 and 60 under 35 U.S.C. 102(e) as being anticipated Schultz et al. (the '575 reference) is withdrawn in light of Applicants' amendment to claim 44.

The rejection of Claims 44, 45, 59 and 60 under 35 U.S.C. 102(e) as being anticipated Chin et al. (the '049 reference) is withdrawn in light of Applicants' amendment to claim 44.

New Ground of Rejection, Necessitated by Amendment

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44, 45, 59 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Written Description Training Materials, Revision 1, March 25, 2008.

Claim 44, the independent claim of the instant invention has been amended and is now drawn to an isolated nucleic acid comprising at least one selector codon that is recognized by an orthogonal translation system and wherein the polynucleotide is translated by the translation system to produce a four helical bundle (4HB) polypeptide agonist selected from the group consisting of human growth hormone, interferon, erythropoietin, and granulocyte cell stimulating factor, and wherein said orthogonal translation system translates the selector codon for a non-naturally encoded amino acid, and wherein the 4HB polypeptide agonist has increased agonist activity as compared to a wild type 4HB polypeptide of the same type.

Thus, the claims are broadly drawn to an isolated nucleic acid which encodes a polypeptide selected form the group consisting of human growth hormone, interferon, erythropoietin, and granulocyte cell stimulating factor, said polypeptide comprising a non-naturally encoded amino acid, said polypeptide having increased agonist activity compared to a wild type polypeptide of the same type.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a genus, the genus being an isolated polynucleotide that encodes a 4HB polypeptide selected form the group consisting of human growth hormone, interferon, erythropoietin, and granulocyte cell stimulating factor, said polypeptide comprising a non-naturally encoded amino acid, said polypeptide having increased agonist activity compared to a wild type polypeptide of the same type.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus.

The specification provides no working or prophetic examples of such polypeptide agonists. The disclosure provides specific teachings only of agonist hGH sequences with disclosed modifications: "Agonist hGH sequences include, e.g., the naturally-occurring hGH sequence comprising the following modifications H18D, H21N, R167N, D171S, E174S, I179T. .... Additional agonist hGH sequences include H18D, Q22A, F25A, D26A, Q29A, E65A, K168A, E174S; H18A, Q22A, F25A, D26A, Q29A, E65A, K168A, E174S; or H18D, Q22A, F25A, D26A, Q29A, E65A, K168A, E174A. ..... **hGH polypeptides comprising substitutions at H18A, Q22A, F25A, D26A, Q29A, E65A, K168A, E174A enhance affinity for the hGH receptor at site I** [paragraphs 0119 and 0120 of US 20080300163, the PGPUB of the instant invention, Emphasis added by the Examiner]. However, the specification does not disclose any examples of substitutions of a non-naturally encoded amino acid at any of these disclosed positions. Thus, insufficient guidance is presented to the practitioner as to the relationship between positions at which non-naturally encoded amino acids may be substituted so that the resulting polypeptide exhibits the required biological activity, which is increased agonist activity as compared to the wild-type polypeptide of the same type.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is an isolated polynucleotide that encodes a 4HB polypeptide selected form the group consisting of human growth hormone, interferon, erythropoietin, and granulocyte cell stimulating factor, said polypeptide comprising a non-naturally encoded amino acid, said polypeptide having increased agonist activity compared to a wild type polypeptide of the same type.

The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential methods of constructing the polynucleotide. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 44, 45, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (the '575 reference) or Chin et al. (the '049 reference), either reference, in view of Spetea et al (1997. Neuropeptides 31:483-488).

The '575 reference teaches an isolated nucleic acid comprising at least one selector codon, wherein the selector codon may be the amber codon; the selector codon, which may be an amber codon, when translated, inserts an unnatural amino acid [paragraph 0031]. The isolated nucleic acid encodes a therapeutic protein which may be an interferon, erythropoietin (EPO), G-CSF or human growth hormone [paragraph 0033]. The '575 reference teaches using translation systems that can incorporate unnatural amino acids into protein [paragraph 0024]. Typically, the O-RS preferentially aminoacylates the O-tRNA with at least one unnatural amino acid in the translation system and the O-tRNA recognizes at least one selector codon, as recited by claim 60. The translation system thus inserts the unnatural amino acid into a protein produced in the system, in response to an encoded selector codon [paragraph 0025]. The

translation systems include host cells, such as bacterial cells (e.g., Escherichia coli), archeaebacterial cells, eukaryotic cells (e.g., yeast cells, mammalian cells, plant cells, insect cells) [parargraph 0026]. The translation system is provided with at least one nucleic acid comprising at least one selector codon, wherein the nucleic acid encodes the at least one protein, an orthogonal tRNA (O-tRNA), that functions in the translation system and recognizes the at least one selector codon and an orthogonal tRNA synthetase (O-RS) [paragraph 0036]. Additionally, the reference teaches that proteins that include an unnatural amino acid can have enhanced or even entirely new properties including enhanced ability to react with other molecules, e.g., covalently or noncovalently [paragraphs 0153 and 0172].

The ‘049 reference teaches a nucleic acid that comprises a polynucleotide that encodes a polypeptide of interest [paragraph 0016] which may be an interferon, erythropoietin (EPO), human growth hormone, and a G-CSF, which are all polypeptides disclosed as 4HB polypeptides by the specification of the instant invention [paragraph 0038]. The polynucleotide comprises a selector codon that is recognized by the O-tRNA. The selector codon may be an amber codon, an ochre codon, or an opal stop codon [paragraph 0047]. The ‘049 reference teaches compositions of orthogonal tRNAs, orthogonal synthetases and pairs thereof, in eukaryotic cells and methods of producing proteins in eukaryotic cells that include unnatural amino acids [paragraph 0003]. The eukaryotic cell comprises an orthogonal tRNA synthetase (O-RS), an orthogonal tRNA (O-tRNA), and a nucleic acid that comprises a polynucleotide that encodes a polypeptide of interest [paragraph 0016]. The ‘049 reference teaches methods for producing, in a eukaryotic cell, at least one protein comprising at least one unnatural amino acid. The methods include, growing, in an appropriate medium, a eukaryotic cell that comprises a nucleic acid that comprises at least one selector codon and encodes the protein of interest. The eukaryotic cell also comprises an orthogonal tRNA (O-tRNA) that functions in the cell and recognizes the selector codon and an orthogonal tRNA synthetase (O-RS) [paragraph 0042]. Additionally, the reference teaches “The incorporation of an unnatural amino acid can be done to….tailor changes

in protein structure and/or function…. Proteins that include an unnatural amino acid can have enhanced or even entirely new catalytic or physical properties. For example, the following properties are optionally modified by inclusion of an unnatural amino acid into a protein: …. ability to react with other molecules, e.g., covalently or noncovalently, …... [paragraph 0200].

Neither '575 reference or the '049 reference, singularly or in combination, teach a nucleic acid encoding a polypeptide comprising a polypeptide agonist comprising a non-naturally encoded amino acid with increased agonist activity as compared to a wild type polypeptide.

Spetea et al. teach analogues of deltorphin peptides, comprising substitutions of Phe with a non-naturally encoded amino acid 2-aminotetralin-2-carboxylic acid (Atc) (page 484, 1st column, 1st paragraph). The new deltorphin I and II analogues were found to exhibit better affinities for their cognate receptors than do their parent compounds, deltorphin I and deltorphin II, respectively. Replacement of Phe at position 3 in the message domain with a synthetic amino acid, Atc, gave rise to more active agonist deltorphin (page 486, 2nd column, last paragraph, bridging page 487 1st column, 1st paragraph).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '575 or '049 reference, which teach nucleic acids encoding 4HB polypeptide agonists comprising non-naturally encoded amino acid residues and construct nucleic acids encoding 4HB polypeptide agonists comprising non-naturally encoded amino acid residues wherein the polypeptides give rise to more active agonist molecules as taught by Spetea et al. The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because the '575 and '049 references teach that the inclusion of an unnatural amino acid into a protein may enhance the ability of the polypeptide to react with other molecules (i.e., cognate receptors) and Spetea et al. teaches that incorporation of non-naturally encoded amino acids (unnatural amino acids) into peptides give rise to more active agonist peptides.

Applicants traverse the rejection as previously presented (Remarks of 26 January 2011, page 12) (The rejections of Claims 44, 45, 59, and 60 under 35 U.S.C. §102(e) as being anticipated by Schultz (US Patent Publication No. 2003/0082575) or Chin (US Patent Publication No. 2005/0009049). Applicants argue that claim 44 has been amended to recite that the 4HB polypeptide is an agonist with increased agonist activity over that of the wild type protein. Neither the '575 reference or the '049 reference teaches production of any 4HB or 4HB polypeptides that have increased agonist activity.

Applicant's arguments have been fully considered but are not found to be persuasive. In light of Applicants' amendment to Claim 44, the rejections have been recast as rejections under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (the '575 reference) or Chin et al. (the '049 reference), either reference, in view of Spetea et al (1997. Neuropeptides 31:483-488).

Conclusion:

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SHULAMITH H. SHAFER/
Primary Examiner, Art Unit 1647